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# Safety of Ketamine in the Prehospital Setting

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## AUTHORS

Author roles, affiliations, and contributions (using the [CRediT taxonomy](#)) are listed below.

Author	Role and Affiliation	Report Contribution
Johanna K. Anderson, MPH	Senior Research Associate, Evidence Synthesis Program (ESP) Coordinating Center, Portland VA Health Care System Portland, OR	Conceptualization, Methodology, Investigation, Data Curation, Formal analysis, Writing – original draft, Writing – review & editing, Project administration
Erin H. Beech, MA	Senior Research Associate, ESP Coordinating Center, Portland VA Health Care System Portland, OR	Conceptualization, Methodology, Investigation, Data curation, Formal analysis
Katherine M. Mackey, MD, MPP	Director & Clinician Investigator, ESP Coordinating Center, Portland VA Health Care System Portland, OR	Conceptualization, Methodology, Investigation, Formal analysis, Funding acquisition, Writing – original draft, Writing – review & editing, Supervision

## PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to conduct timely, rigorous, and independent systematic reviews to support VA clinicians, program leadership, and policymakers improve the health of Veterans. ESP reviews have been used to develop evidence-informed clinical policies, practice guidelines, and performance measures; to guide implementation of programs and services that improve Veterans' health and well-being; and to set the direction of research to close important evidence gaps. Four ESP Centers are located across the US. Centers are led by recognized experts in evidence synthesis, often with roles as practicing VA clinicians. The Coordinating Center, located in Portland, Oregon, manages program operations, ensures methodological consistency and quality of products, engages with stakeholders, and addresses urgent evidence synthesis needs.

Nominations of review topics are solicited several times each year and submitted via the [ESP website](#). Topics are selected based on the availability of relevant evidence and the likelihood that a review on the topic would be feasible and have broad utility across the VA system. If selected, topics are refined with input from Operational Partners (below), ESP staff, and additional subject matter experts. Draft ESP reviews undergo external peer review to ensure they are methodologically sound, unbiased, and include all important evidence on the topic. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. In seeking broad expertise and perspectives during review development, conflicting viewpoints are common and often result in productive scientific discourse that improves the relevance and rigor of the review. The ESP works to balance divergent views and to manage or mitigate potential conflicts of interest.

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### *Operational Partners*

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

### **Douglas Villard, MD**

*Director of Emergency Ambulance Services*  
National Emergency Medicine Office

## DISCLOSURES

This report was prepared by the ESP Center located at the **VA Portland Health Care System**, directed by Katherine Mackey, MD, MPP, and funded by the Department of Veterans Affairs, Veterans Health Administration, Health Systems Research.

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# *Executive Summary*

## KEY FINDINGS

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- ▶ Evidence on mortality following ketamine administration for acute pain, sedation, or rapid sequence intubation (RSI) in the prehospital setting is limited to observational data from 3 studies. These studies did not find a significant difference in mortality among patients who received ketamine for acute pain, sedation, or RSI compared to other medications commonly used in the prehospital setting for these indications. However, this evidence should be considered preliminary as it is limited to a small number of studies with variable patient populations, comparators, co-interventions, and outcome definitions.
- ▶ Among studies of prehospital ketamine administration for acute pain or sedation, the incidence of serious adverse events was generally low and did not significantly differ between ketamine and comparator medications.
- ▶ A large controlled observational study reported a higher incidence of invasive airway placement and severe oxygen desaturation among patients who received ketamine compared to benzodiazepines or antipsychotics for acute behavioral disturbance in the prehospital setting. However, 2 smaller cohorts did not find that receipt of ketamine for prehospital sedation was associated with higher intubation incidence. Further research is needed to clarify the potential increased risk of intubation when ketamine is used for sedation in the prehospital setting given the inconsistent findings of existing studies.
- ▶ Whether the risk of hypotension is different with ketamine compared to etomidate for RSI is unclear due to inconsistent findings in a small number of observational studies. Relative to studies of ketamine for acute pain and sedation, the safety of ketamine for RSI in the prehospital setting has been less frequently studied and represents an important area for future research.
- ▶ The risk of some adverse events may increase with higher ketamine doses (> 2mg/kg intravenous/intraosseous or > 5mg/kg intramuscular) based on observational studies of ketamine for sedation and RSI.
- ▶ In the prehospital setting, ketamine appears to be at least as effective for acute pain reduction compared to opioids. Ketamine also appears to be at least as effective as benzodiazepines for prehospital sedation and at least as effective as etomidate for prehospital RSI.

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Ketamine is a dissociative anesthetic with a long history of use for procedural sedation and anesthesia in the hospital setting. Ketamine is also increasingly used for acute pain, sedation, and rapid sequence intubation (RSI) in the prehospital setting according to national and state emergency medical services (EMS) protocols. Use of ketamine for these indications is broadly supported by guidelines and position statements from multiple professional societies.

Ketamine has several pharmacologic properties that make it well suited for use in the prehospital setting. In addition to causing neuro-inhibition and anesthesia through antagonism of NDMA receptors, ketamine is active at opioid receptors and provides rapid onset analgesia at low doses. It also has effects at catecholamine receptors, which make it a favorable agent to use for RSI because it leads to increases in heart rate, contractility, and mean arterial pressure. Ketamine has multiple routes of

administration, adding to its usefulness in a range of clinical scenarios. However, ketamine's versatility has also led to concerns that it could be overused or inappropriately used in the prehospital setting, potentially exposing patients to unnecessary risk of harms.

Several existing systematic reviews have examined the use of ketamine in the prehospital setting for acute pain, sedation, and RSI and have generally found that ketamine is safe and effective when used appropriately. However, these reviews have largely included studies conducted in the emergency department (ED) and extrapolated findings to the prehospital setting. More evidence specific to the prehospital setting is becoming available as EMS providers seek to improve guidance for the field and ensure the safety of EMS treatment protocols.

## CURRENT REVIEW

The VA Evidence Synthesis Program Coordinating Center (ESP CC) is responding to a request from the VA National Emergency Medicine Office (NEMO) for a review of evidence on the safety of ketamine for acute pain management, sedation, and RSI in the prehospital setting. Findings will be used to inform national protocols for VHA paramedics and EMTs.

Among 1,652 potentially relevant articles identified through systematic literature searches, 49 studies met eligibility criteria and were included in this review. We prioritized synthesis of 24 comparative studies (randomized controlled trials [RCTs] and cohort studies that adjusted for baseline group differences) as the most rigorous and informative evidence. These 24 studies included 13 studies of ketamine for acute pain management, 6 for sedation in cases of acute behavioral disturbance, 4 for RSI, and 1 study that did not specify the indication for ketamine.

Evidence regarding mortality following ketamine administration in the prehospital setting is limited to 3 retrospective cohorts, none of which found a significant difference between patients receiving ketamine compared to other medications. However, this evidence should be considered preliminary given the small number of studies, variability across studies in patient populations, indications for ketamine, co-interventions and comparator medications, and outcome definitions.

Across studies, rates of other serious adverse events were low. Two retrospective cohorts, including 1 large cohort ( $N = 7,973$ ), of patients with acute behavioral disturbance who received ketamine for sedation did not find a significant difference in cardiac arrest rates (reported as a stand-alone outcome and not as part of a composite outcome) with ketamine compared to other medications. However, the same large retrospective cohort ( $N = 7,973$ ) found that the incidence of invasive airway placement and severe oxygen desaturation were significantly higher for those who received ketamine compared with benzodiazepines or antipsychotics. Two smaller retrospective cohorts did not find a significant difference in the need for invasive airway placement when ketamine was used for sedation.

When ketamine is compared to opioids or placebo for acute pain, it may be associated with a higher incidence of non-serious adverse events including emergence phenomenon, neuropsychological effects, sedation, dizziness, and visual disturbance. No differences were observed for other outcomes including respiratory problems, arrhythmias, hypertension, or nausea and vomiting. Other adverse events were reported only in a single study or had inconsistent findings across studies. The figure below presents the direction of findings for adverse event incidence with ketamine compared to other medications given in the prehospital setting for acute pain, sedation, and RSI.

## ES Figure: Direction of Findings for Adverse Event Incidence with Ketamine versus Comparators

Adverse Event <sup>a</sup>	Acute Pain	Sedation	RSI
Any	?		
Cardiac arrest		↔	
Advanced airway placement or O2 need		⊕	
Respiratory problems ( <i>eg</i> bradypnea)	↔		
Arrhythmia	↔		
Hypertension	↔		
Hypotension	↔		?
Nausea and/or vomiting <sup>b</sup>	↔		
Emergence phenomena	⊕		
Feeling of unreality	↔		
Hallucinations or mood change	↔		
Neuropsychological effects	⊕		
Sedation	⊕		
Dizziness	⊕		
Itching	↔		
Visual disturbance	⊕		
Other (fatigue, general discomfort, hearing changes, headache)	↔		

*Notes.* <sup>a</sup> This table only includes outcomes reported in at least 2 studies examining the outcome for the same ketamine indication with the same comparator. A double-sided arrow indicates no difference. A plus sign indicates a higher incidence. A question mark indicates an unclear direction of findings. A light blue shaded box indicates low strength of evidence. A dark blue shaded box indicates moderate strength of evidence. An orange box indicates unclear findings due to insufficient evidence. A gray shaded box indicates no available data.

<sup>b</sup> Strength of evidence was low for ketamine versus placebo and moderate for ketamine versus morphine.

*Abbreviations.* O2=oxygen; RSI=rapid sequence intubation.

Higher dose ketamine (> 2mg/kg intravenous/intraosseous or > 5mg/kg intramuscular) led to increased rates of intubation among patients receiving prehospital ketamine for sedation and increased rates of hypotension, bradycardia, oxygen desaturation, laryngospasm, and agitation among patients receiving prehospital ketamine for RSI. However, these findings are limited to a single study for each indication and further research is needed to confirm results.

Across indications, prehospital ketamine appears to be at least as effective as other medications for pain control, sedation, and RSI. Prehospital ketamine resulted in similar or higher levels of pain relief compared to opioids in patients requiring prehospital pain control. Likewise, prehospital ketamine was more or similarly effective for prehospital sedation and RSI compared to other medications used for these indications.

Although we identified a large body of evidence on this topic, studies varied widely by ketamine indication, comparators, and outcomes, making it difficult to reach strong conclusions about ketamine's safety. Additionally, half of the included studies lacked a comparison group or did not adequately control for baseline differences between intervention groups, limiting our ability to understand whether benefits and harms differed based on receiving ketamine or could be explained by other factors. Future research powered to detect differences in mortality and cardiac arrest rates would help to further establish ketamine as a safe option for prehospital use. Because patient deaths and cardiac arrest are rare events, large-scale database studies, such as those conducted within VHA, may be best suited to evaluate these outcomes. Additionally, future research could help to clarify the risk of adverse events when ketamine is used for sedation in cases of acute behavioral disturbance, specifically whether ketamine used for this indication is associated with an increased incidence of intubation or severe oxygen desaturation. The most informative studies to address this question would be RCTs or cohort studies that adjust for baseline differences between groups. Finally, given the higher potential for adverse events with higher doses of ketamine, future research could focus on determining the minimum effective doses for certain indications such as sedation, identifying best practices to accurately assess patient weight in the prehospital setting, and implementation efforts to ensure that existing protocols regarding ketamine dosing are followed.

## CONCLUSIONS

Ketamine has been broadly incorporated into national and state EMS protocols for the management of patients with urgent and emergent conditions and has a long history of use as a medication for procedural sedation and anesthesia in the hospital setting. In general, based on existing evidence, ketamine does not appear to increase the risk of serious adverse effects compared to other medications used for acute pain management, sedation, and RSI in the prehospital setting, with the exception of a potentially higher rate of intubation and severe oxygen desaturation with ketamine when used for acute behavioral disturbance. However, the evidence is limited by study methodological weaknesses, variability in co-interventions and comparators, and differences in how harms were reported across studies. Evidence on mortality was limited to 3 retrospective cohorts with varying patient populations, comparators, and outcome definitions and should be considered preliminary. Large database studies could help to confirm that prehospital administration of ketamine is associated with a relatively low risk of mortality or cardiac arrest (rare events overall) compared to alternative medications. RCTs or well-designed cohort studies would provide further insight into the potential risks of ketamine for sedation in cases of acute behavioral disturbance.